Compassionate Use Experience with High Titer RSV Immunoglobulin (RSV-IVIG) in RSV Infected Immunocompromised Persons

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Introduction

Respiratory syncytial virus (RSV) may cause severe disease in persons with compromised immune function. Recipients of lung or hematopoietic stem cell transplant (HSCT) are at particularly high risk of severe RSV infection with mortality rates of 20% to 40% for those who develop lower respiratory tract infection (LTRI). Optimal therapy for immunocompromised patients with RSV infection has not been defined. Ribavirin has been used off label in oral, intravenous and inhaled formulations in immunocompromised patients with RSV, despite questionable efficacy. A second option for treatment of RSV infection is immunoglobulin, generally combined with ribavirin. There are two immunoglobulin products, palivizumab and pooled human intravenous immunoglobulin (IVIG). Because of the cost palivizumab, IVIG is generally used in adults when an immunoglobulin product is needed. RI-001 (ADMA Biologics, Inc.) is an IVIG prepared from donors selected to have high titer neutralizing anti-RSV antibody. We report its use on a compassionate use basis in patients with lower tract RSV disease who failed conventional therapy or were at high risk for progression of RSV infection.

Method

Patients

Data were collected from patients who received compassionate use RI-001 at 6 centers in the US, 3 centers in Australia, and 1 center in New Zealand from December 2008 to February 2011. Hospitalized patients with documented RSV who were either unresponsive to standard of care therapy including some combination of ribavirin, corticosteroids, palivizumab or standard IVIG or who were at high risk for mortality due to their RSV infection were eligible. Serum samples were requested prior to infusion and 1, 3, 8 and 18 days post infusion for measurement of serum RSV neutralizing antibody titers.

Study Product

RI-001 is polyclonal human IgG made from pools of source plasma from up to 300-400 screened healthy US adult donors with high neutralizing anti-RSV titers. The immunoglobulin pool contains standardized high levels of RSV neutralizing antibodies, consisting of various immunoglobulins specificities representative of the diversity of human antibodies made against the virus. Product was provided as part of a compassionate use study, on an emergency use basis by ADMA Biologics, Inc., Ramsey, NJ.

Product Infusion

Patients were treated on day 1 with RI-001 1500mg/kg, followed 2 days later with 750 mg/kg on day 3. RI-001 drug concentration was 100 mg/mL. Infusion rate was gradually increased from 0.3 mL/kg/hour to 2.0 mL/kg/h (maximum 150 mL/h) over a 2 hour period. If an infusion reaction occurred, infusions were slowed or stopped until symptoms resolved and then re-started at a lower rate.

Microneutralization Antibody Assay

Serum neutralizing-antibody titers were performed by microneutralization method for RSV A strain. Serum dilutions were incubated with -75 pfu of RSV A2 strain for 30 minutes at room temperature, followed by the addition of 1.5 x 104 HEp-2 cells in 96-well culture plates. After 3 days, the quantity of RSV antigen was determined by EIA using MAb to the RSV F protein. The neutralization titer was defined as the serum dilution that results in a 50% reduction in color development.

Statistical Analysis

Means between groups were compared by Student's t test; proportions were compared by Fisher's Exact test.

Results

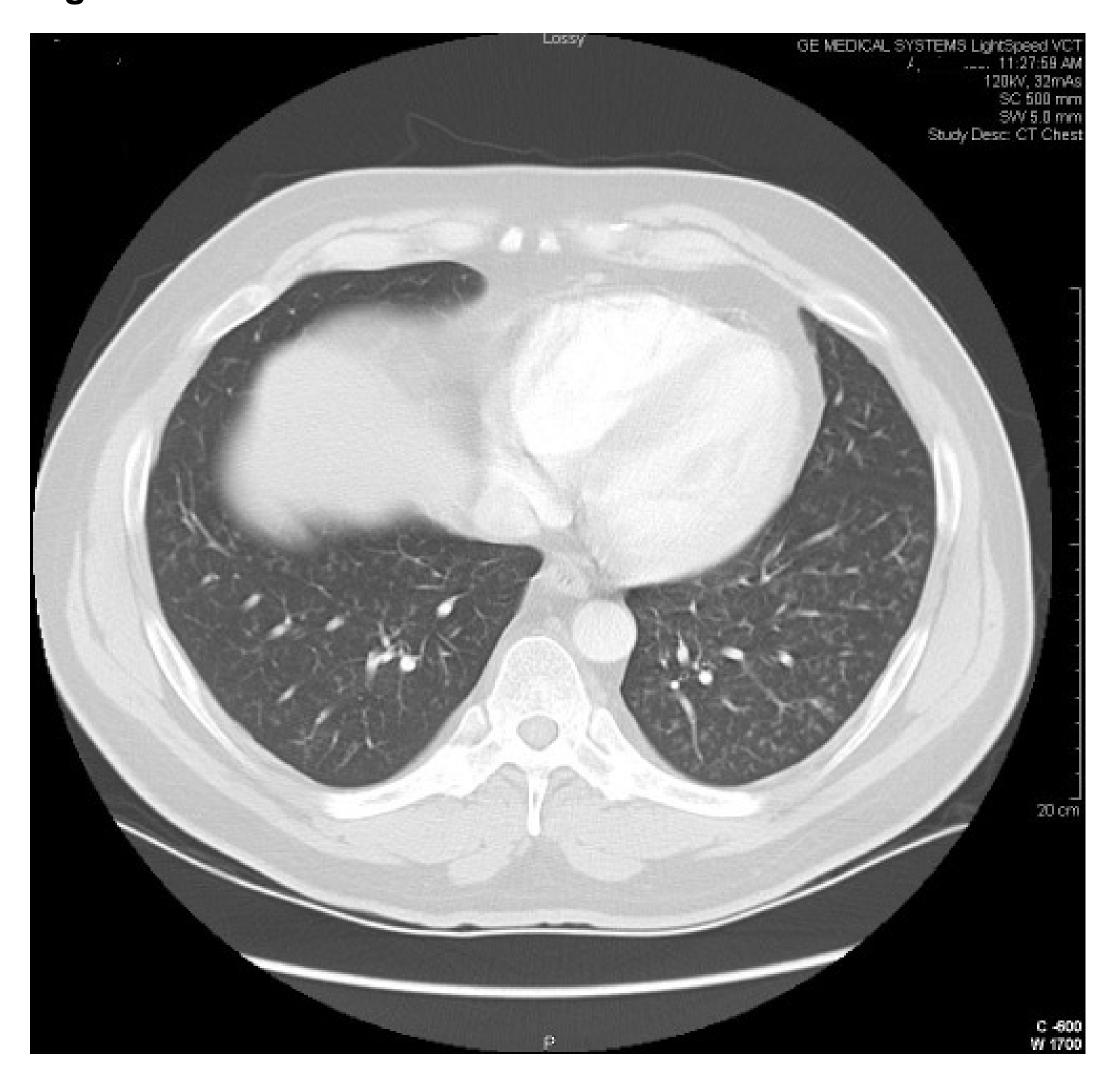
Population: A total of 15 patients ranging in age from 2 months to 71 years of age received compassionate use RI-001 (Table 1). Patients with a variety of underlying medical conditions received RI-001 including: recipients of bone marrow transplants or HSCT (9), hematologic malignancy (3), severe combined immunodeficiency [SCID] (1), Liver transplant (1), and interstitial lung disease (1). Four HSCT recipients were pre-engraftment and 3 had chronic graft versus host disease (GVHD) at the time of RSV infection. All but one patient was felt to have pneumonia or LRTI due to RSV. A variety of radiographic changes were reported with bilateral or diffuse involvement with ground glass or interstitial infiltrates being most common. Co-infections during RSV infection were frequent (7/15). All received ribavirin prior to or concomitant with RI-001 treatment. Seven were treated with inhaled, 4 with intravenous, 1 with oral and 3 with a combination of oral and inhaled ribavirin. Eight patients received prior antibody treatments; 6 received standard intravenous immunoglobulin (IVIG) and 4 children received palivizumab (2 with IVIG) and one patient received IVIG after RI-001.

Table 1: Patient Characteristics

Subject Number	Age	Sex	Underlying Disease	CXR/CT Scan	Low SaO2	RSV Clinical Diagnosis	Other RSV Therapy	Co-infection
1	59	M	Hepatitis C, liver transplant x2, ESRD on dialysis, CHF	Diffuse nodular ground glass infiltrates, right mid lung consolidation	92	Pneumonia	Inhaled Ribavirin	None
2	66	F	Re induction chemotherapy, relapsed AML	Diffuse interstitial infiltrates	93	Pneumonia	Inhaled Ribavirin, IVIG	None
3	44	M	CLL	Diffuse tree and bud	93	Bronchiolitis/ Pneumonia	Inhaled Ribavirin	None
4	2	F	ALL, post BMT 10 months prior, GVHD	Bilateral atelectasis and consolidation	88	Pneumonia	IV Ribavirin, IVIG	Clostridium difficile
5	8	F	AML HSCT pre engraftment	Left sided diffuse alveolar opacities	85	Pneumonia	IV Ribavirin	Clostridium difficile
6	46	M	AML HSCT 2 years prior hypogammglobulinemia chronic GVHD	Bronchiectasis ground glass infiltrates	93	LRTI	Oral Ribavirin, IVIG	None
7	9	M	ALL cord blood HSCT pre engraftment	NA	94	LRTI	IV Ribavirin, IVIG	Blood culture CONS
8	47	M	ALL, HSCT 11 months prior, GVHD	Diffuse patchy opacities CT- ground glass	92	Pneumonia	Inhaled & Oral Ribavirin	None
9	1.5	M	HLH persistent RSV HSCT pre engraftment	Clear	100	Persistent RSV	IV Ribavirin, Palivizumab	None
10	.75 months	M	Osteopetrosis RSV prior to HSCT	Bilateral opacities, interstitial markings	79	Pneumonia	Inhaled & po Ribavirin, Palivizumab, IVIG	HMPV, HRV, CONS, lactobacillus
11	.17 months	M	SCID	RUL infiltrate	89	Pneumonia	Inhaled Ribavirin, Palivizumab, IVIG	CONS
12	20	F	APML prior BMT HSCT pre engraftment	Diffuse ground glass small nodules	pO2-55	Pneumonia	Inhaled Ribavirin, IVIG	None
13	.92 months	F	ALL, seizures, history of pulmonary aspergillus	Bilateral patchy infiltrates	NA	Pneumonia	Inhaled Ribavirin, Palivizumab	None
14	71	F	Interstitial lung disease	Diffuse interstitial alveolar infiltrates	81	Pneumonia	Inhaled Ribavirin	Influenza A
15	15	M	Aplastic anemia PNH HSCT	Bilateral lower lobe infiltrates	93	Pneumonia	Oral & Inhaled Ribavirin	Clostridium difficile

CXR = Chest radiograph, CT = Computerized tomography, SaO2 = Percutaneous oxygen saturation, CHF = Congestive heart failure, NPS = Nasopharyngeal swab, ESRD = End stage renal disease, AML= Acute myelogenous leukemia, IVIG = intravenous immunoglobulin, CLL = Chronic lymphocytic leukemia, PCR = polymerase chain reaction, ALL = Acute lymphocytic leukemia, BMT = bone marrow transplant, GVHD = Graft versus host disease, NPA = nasopharyngeal aspirate, IFA = immunofluorescent assay, HSCT = hematopoietic stem cell transplant, LRTI = lower respiratory tract infection, BAL = bronchoalveolar lavage, CONS = coagulase negative staphylococcus, HMPV = human metapneumonvirus, HRV = human rhinovirus, SCID = severe combined immunodeficiency

Figure 1



Case Report: Tree-in-bud RSV Bronchiolitis Subject #3

The patient is a 44 yo man with CLL undergoing intensive chemotherapy. In April the patient developed a URI. He was initially febrile with nasal and ear symptoms which slowly resolved but he developed progressive dyspnea and a productive cough after 10 days of illness. Chest CT showed diffuse bronchiolitis. He was seen in the infectious disease clinic on illness day 10 and RT-PCR of his sputum sample was positive for a high titer of RSV group B. He was pale and dyspneic with diffuse wheezes and rales on lung exam. Oxygen saturation dropped from 97% to 93% on RA during minimal exercise. Because he remained ill and required additional chemotherapy in the near future he was admitted to the hospital for treatment. On admission he received RSV IVIG at 1500mg/kg (day 1) and 750mg/kg on day 3. By day 4 his wheezing had resolved and was feeling much improved. Oxygenation normalized and he was discharged on day 5. He was seen in clinic over the following 2 weeks and was doing well. The patient began chemotherapy for his CLL 3 weeks after treatment and had no recurrence of RSV.

RI-001 Treatment

14 patients received 2 doses of RI-001 and 1 patient received 4 doses of RI-001 at 1500 mg/kg on days 1, 3, 5 and 7. Three patients were judged to have infusion related adverse events (AE) (Table 2). All resolved after slowing the infusion and tolerated the second dose with premedication.

Illness Outcomes

Of the 15 patients treated, 7 required ICU treatment, 6 assisted ventilation [2 non-invasive and 4 mechanical ventilation] during their RSV infection (Table 2). All patients requiring mechanical ventilation died and 3 of the 4 had respiratory failure prior to receipt of RI-001. Eleven of 15 (73%) patients had improvement of their respiratory infection and survived the hospitalization. No differences in survival were observed in patients who had undergone bone marrow or HSCT versus those who had not. Survival was 0/4 (0%) for patients with respiratory failure compared to 11/11 (100%), p<.001 in those without respiratory failure.

Table 2: Illness Outcomes

Subject Number	Days from Initial Symptoms to RI-001	Days from New Onset Symptoms to RI-001	Days from RSV Diagnosis to RI-001	ICU	Assisted Ventilation	Survival	Infusion Adverse Event	Follow up RSV Testing
1	30	21	6	No	No	Yes	Back pain, ↑ BP - 1st infusion, 2nd well tolerated without premeds Day 42 negative	
2	9	9	8	Yes	BIPAP	Yes	None	NA
3	13	13	1	No	No	Yes	Back pain, ↑ BP, hives, stiff neck - 1st infusion, 2nd well tolerated with premed	Day 27 negative
4	11	11	5	No	No	Yes	None	Day 5, 9, 14, 18 negative
5	11	3	2	Yes	CPAP	Yes	None	NA
6	10	10	3	No	No	Yes	None	Day 13 positive, weekly after all negative
7	19	19	2	No	No	Yes	Abdominal pain, flush, nausea, mild rash 1st dose, 2nd well tolerated with premed	Day 28 BAL positive, Day 34 negative
8	5	5	3	No	No	Yes	None	NA
9	49	7	3	No	No	Yes	None	NA
10	55	55	50	Yes	Mechanical Ventilation	No	None	Post mortem viral culture negative
11	48	10	10	Yes	No	Yes	None	NA
12	11	11	7	Yes	Mechanical Ventilation	No	None	Day 28 positive
13	24	24	20	Yes	Mechanical Ventilation	No	None	Day 30, 43 positive
14	48	48	4	Yes	Mechanical Ventilation	No	None	NA
15	10	10	5	No	No	Yes	None	NA

ICU = intensive care unit, BP = Blood pressure, BIPAP = Bilevel positive airway pressure, NA= Not available, CPAP= continuous positive airway pressure

Timing of RI-001

Time from onset of respiratory symptoms and time from RSV diagnosis to initiation of RI-001 treatment were evaluated (Table 3). Patients were evaluated in 2 ways; time from onset of any respiratory symptom and time from new respiratory symptoms relating to RSV infection. Time from RSV diagnosis and from onset of new respiratory symptoms to treatment with RI-001 was significantly shorter among survivors compared to non-survivors.

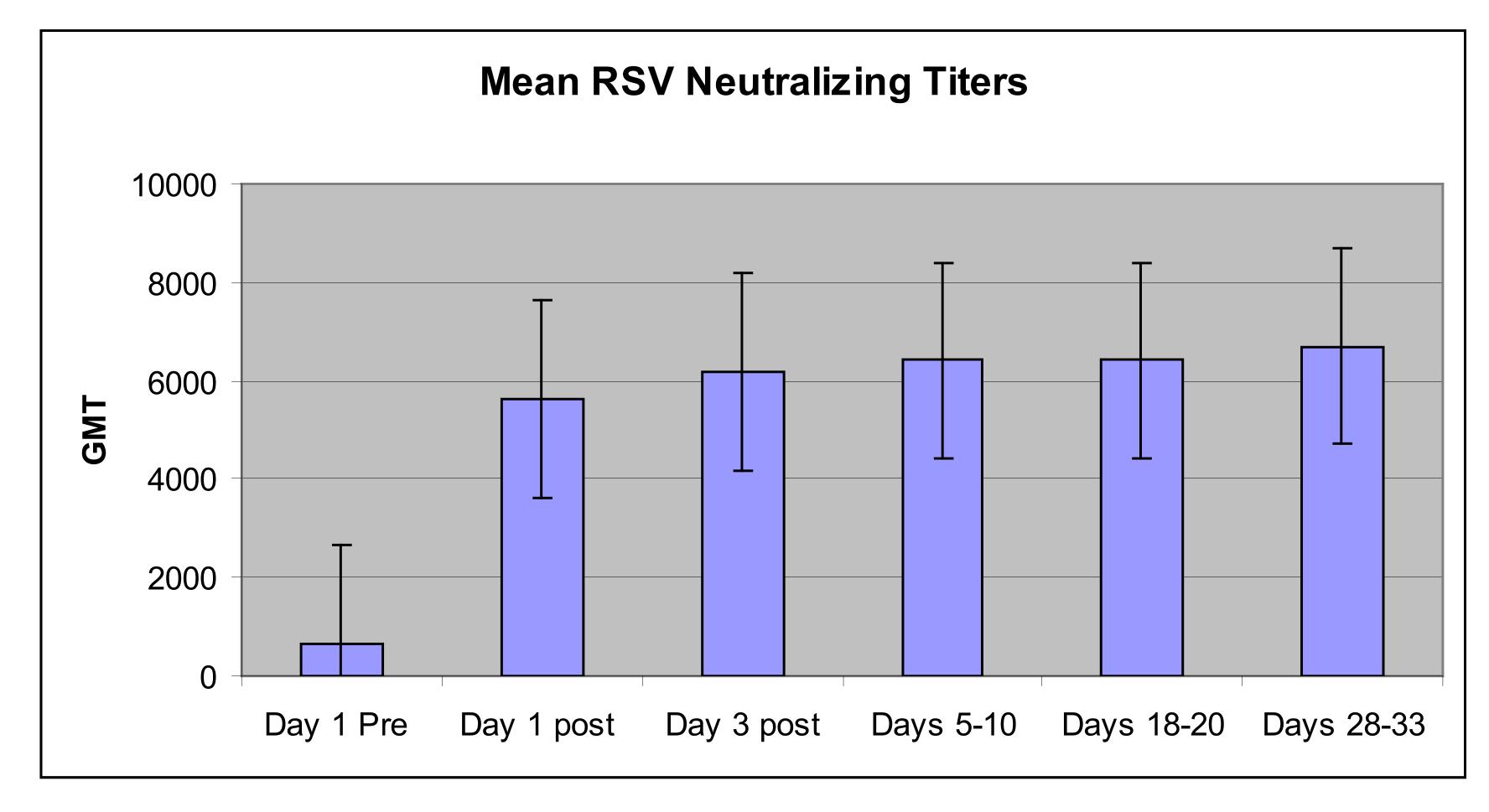
Table 3: Timing of RI-001 Treatment

Time to Treatment with RI-001 Mean (Standard Deviation)	Survived N=11	Died N=4	P Value
Days from initial respiratory symptoms	19.5 (15.8)	34.5 (20.5)	0.15
Days from new respiratory symptoms	10.7 (5.4)	34.5 (20.5)	.003
Days from diagnosis of RSV	4.4 (2.8)	20.3 (21.0)	.02

Antibody Measurements

Fourteen patients had pre-treatment and at least one post infusion serum sample available for measurement of serum neutralizing antibody against RSV. The pre infusion titers ranged from 51 to 1765 GMT with a mean of 646 ± 519. All patients demonstrated at least a 4-fold rise post infusion. The increases between mean GMT titers from baseline compared to days 1, 3 and 5-10 post infusion were all significantly higher (5625 ± 3109, 6176 ± 4061, 6410 ± 4470, respectively, all p<0.0001) (Figure 2).

Figure 2



Discussion

Optimal treatment of RSV infection in this population is controversial primarily due to the lack of definitive randomized controlled trials. However, several retrospective studies and a recent pooled analysis suggesting that ribavirin in any form is associated with decreased progression of URTI to LRTI (45% to 16%) and decreased mortality (70% to 13%). Immunotherapy is an option for adjunctive therapy with antiviral agents for the treatment of RSV infection in immunosuppressed persons. In addition to an antiviral effect, immunoglobulins are known to have anti-inflammatory effects which may be beneficial when used in combination with antiviral agents. In a review of 407 HSCT patients, treatment with aerosolized ribavirin plus either IVIG, palivizumab or high titer RSV immunoglobulin (RespiGam®), Shah and Chemaly noted a trend towards decreased progression from URTI to LRTI and significantly lower mortality in those who received dual treatment compared to those treated with ribavirin alone.

Our experience with 15 patients who received RI-001 as compassionate use indicates the product is safe and well tolerated with minimal side effects. RI-001 produced at least a 4-fold rise in RSV neutralizing titers in all patients, and in some had 24 to 76 fold increases. These results highlight the advantage of using RI-001 over standard IVIG in achieving high serum.

Conclusions

- RI-001 infusions were safe and well tolerated with minimal side effects
- Administration of RI-001 resulted in significantly higher levels of neutralizing antibody against RSV
- These results suggest that early treatment with RI-001 improves survival in patients with RSV LRTI